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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/814,764	03/31/2004	Eric R. First	17672 (BOT)	8867

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EXAMINER	
PORTNER, VIRGINIA ALLEN	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 12/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/814,764	FIRST, ERIC R.	
	Examiner	Art Unit	
	Ginny Portner	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/20/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-13 are pending.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-5,7-11, 13 are rejected under 35 U.S.C. 112, first paragraph (scope), because the specification, while being enabling for a method of treating or preventing a pressure sore defined to include methods that alleviate at least one symptom associated with a pressure sore, specifically those effects that adversely effect skin due to muscle tension, through administering a specific non-toxic dosage of botulinum neurotoxin, delivered locally to the cite which effects the symptom to be alleviated, does not reasonably provide enablement for the administration of any dosage size to any local location of a mammal in a method of treating any pre-existing pressure sore or preventing any skin area that is predisposed to developing a pressure sore. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The invention claims comprises the step of administering a botulinum toxin to any location that is local to, in the vicinity of or directly into a pressure sore (see all claims and pages 3 and 22-24 for definitions. The definition includes patients with without stage I or with any one of stage I-IV pressure sores (see page 3, entire page).

The dosage amount is any amount that will effectively eliminate a symptom, but the amount is not defined to be non-toxic but may be any amount (see claims 1-5, 7-11, and 13 any amount or any effective amount). The claims broadly recite the administration of a botulinum toxin to any part of a patient's body in or near a pressure sore or a possible location that has the

potential of developing a pressure sore. The claims are not enabled for the administration of a botulinum toxin in any amount or any effective amount to any location to prevent or treat a pressure sore. The administration of any effective amount of a botulinum toxin within, at or near the nerves of the spine, cranium, heart or any other nerves associated with essential organ systems which would effectively induce paralysis, and even death. The definition of "to or to the vicinity a pressure sore" includes extensive portions of the body, and the claims are not limited to the administration of botulinum toxin in an amount that is non-toxic or therapeutically effective.

As Botulinum toxins are among the most toxic substances known for man and have caused blurred vision, dry mouth, constipation, dizziness, abdominal cramps, nausea/vomiting, general weakness, apathetic behavior, orthostatic hypotension, impaired micturition/sexual function, muscle paralysis (US Pat. 5,562,907, col. 1, lines 35-37) and death, complications due to apparent diffusion of the toxin from the infected muscle(s) to adjacent muscles resulting in difficulty in swallowing, stomach feeding, resulting in paralysis (see Pat. 5,562,907, col. 5, lines 38-65 and col. 6, lines 1-14) and toxin leakage induced edema, serum albumin decrease and injury to vascular endothelium (see col. 8, lines 45-65), the local administration of any amount of a Botulinum toxin to any location of a patient (mammal), would not serve to treat a potential or existing pressure sore.

The claims recite the administration of any effective amount of any botulinum toxin to a patient. The person of skill in the art would be required to carry out undue experimentation to utilize any amount of botulinum toxin administered to any site in order to obtain a desired positive therapeutic effect, especially in light of the fact that Botulinum toxins are known to

evidence extensive negative side effects and even death of mammals if the amount of toxin is too high and diffusion of the neurotoxin to additional locations of the brain, would and could result in extensive negative side effects and death of the patient due to inactivation of essential brain nerve functions.

While claims 4 and 10 recite a range of dosage amounts, the cite of administration is any location and need not be administered to nerves that are responsible for the nerve associated muscle tension known to be a cause for pressure sore development or existence.

Additionally the instant specification teaches that the dosage permissible for administration of botulinum toxin A differs from the dosage form for Botulinum neurotoxin B (instant specification). Administration of the same dosage level for every botulinum toxin could result in an undesired systemic effect, and could result in a negative, non-treatment of the patient.

While claims 7-10 define the site of administration to be a pressure point, the amount administered is not so claimed as to enable the animal to evidence a therapeutic effect, without negative side effects; the amount administered is not required to be a non-toxic, therapeutically effective amount, and large amounts of botulinum toxin could result in paralysis or death of the patient.

The botulinum toxin molecule is fully toxic (□ toxin□ recited in claims) to any tissues to which it comes in contact, thus the genus of methods now claimed is not enabled for the full scope in light of the fact that any amount of toxin administered would not serve to treat a pressure sore and would not serve to alleviate at least one symptom of a pressure sore without undesirable, deleterious toxic effects.

The Wands factors have been considered in the establishment of this instant scope of enablement rejection:

1. the quantity of experimentation necessary would be undue for the utilization of any amount of any botulinum toxin administered to any site of a patient, the local site being in the vicinity (definition provided by instant specification for the term □local□) of a desired region;

2. the amount of direction or guidance presented for utilization of dosage amounts not disclosed to be within a non-toxic range, to the specific receptors associated with a pressure sore: the negative side effects could be deleterious to the patient, and would not result in treatment;

3. the presence or absence of working examples utilizing local administration sites other than specific regions associated with specific symptoms to be alleviated have not been provided;

4. the nature of the invention is one that without specific guidance, would result in a method that could result in paralysis of the patient or even death;

5. the state of the prior art is one in which specific sites, and dosage ranges provide a desired result, but administration of any amount to any local site, of any botulinum toxin that would not serve to interact with sympathetic nerve or inhibiting release of acetylcholine from cholinergic parasympathetic nerve endings associated with alleviating symptoms associated with a pressure sore;

6. the relative skill of those in the art: high;

7. the predictability or unpredictability of the art: unpredictable negative side effects when present in undesirable locations, especially locations associated with nerves of the brain, neck, thoracic, lumbar and spinal cord regions of the body which have extensive nerve endings which would be greatly effected, and functionality inhibited (blocked for weeks or months) by the administration of botulinum toxin; and

8. breadth of the claims: broad but definite.

In view of the prior art teaching (reference cited above and specific teachings of the instant specification) that botulinum toxins administered to any location site, in any amount, that may or may not interact with the nerves associated with pressure sores, would not predictably result in the positive desired effect of alleviating at least one symptom of a pressure sore, the instantly claimed invention is enabled only for a scope of what is now claimed.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

2. Claims 1-4, 6-10, 12-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Pohl et al.

Pohl et al disclose a method of treating a pre-existing pressure sore and a method of preventing the pressure sore from becoming worse or preventing additional tissue sore development, the method comprising the step of :

Administering botulinum toxin type A to a patient in a therapeutically effective amount in the vicinity of the pressure sore (see page 36, top of page, Table 1, patient 5), wherein the pressure sore improved from level 4, severe to level 2, much improved.

The amount of botulinum toxin type A administered was a therapeutically effective amount, and would be within the recited ranges of "about 1 to 300 units) or" 5 units to 25,000 units", as dosage was therapeutically effective to reduce stress to the vicinity of the pressure sore and thereby served to treat the existing pressure sore and

served to prevent additional pressure sore development. The reference anticipates the instantly claimed invention.

3. Claims 1-3, 6-9, 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Kennedy, (1997).

Kennedy discloses the instantly claimed invention directed to a method of preventing/treating (preventing) the development of pressure sores, the method comprising the step of :

Administering botulinum toxin type A directly into the spastic muscle (see page 22, col. 2, paragraphs 2-3 "Botox" uses the botulinum neurotoxin, a powerful neurotoxin" "By using it in small amounts, it can be injected directly into spastic muscles, where the nerve attaches to the muscle, blocking the signal"), thus preventing the development of a pressure sore (see page 22, col. 1, last paragraph "Cramping can make patients terribly uncomfortable and can make them immobile, leading to pressure sores").

The reference anticipates the instantly claimed invention.

Please Note: the examiner is reading the term "treating" to encompass the administration of botulinum toxin to patients that do no have a pressure sores (preventing pressure sore development) and to patients that have a pre-existing pressure sore (aiding in the healing process) based upon applicant's definition of treating provided at page 24, lines 15-16; page 23, lines 4-6 and page 3, paragraph 1,) The definitions provided include the administration of botulinum toxin to patients with conditions associated with forces that "cause microcirculatory

occlusion as pressures rise above capillary filling pressure, resulting in ischemia (see page 3, paragraph 1 and page 22, paragraph 1)" and administering botulinum toxin to any region of the body (see page 26, last paragraph), to include administration of botulinum toxin to skin for relieving inflammation (see instant Specification, page 34, paragraph 1).

4. Claims 1-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Gassner et al (US Pat. 6,44,787).

Gassner et al disclose the instantly claimed method that comprises the steps of:

Administering (see col. 3, lines 6-8 and 37-40) botulinum toxin A, B, C, D, E, F or G (see col. 2, lines 8-9) to (see claim 26, "an unfavorable wound" (see Gassner et al claim 27"; omprises subcutaneous tissue administration) a patient to reduce inflammatory skin/wound sores (lesions; this embodiment is included in Applicant's definition of treating and preventing pressure sores).

Additionally Gassner et al disclose the importance of reducing wound healing time, through addressing and preventing: "Repeated microtrauma, caused by continuous displacement of injured tissue," which " induces a prolonged inflammatory response and an increased metabolic activity during the healing process (see col. 1, lines 43-50)." This definition of Gassner et al is analogous to Applicant's definition of the instant invention which addresses treating or preventing those forces that "cause microcirculatory occlusion as pressures rise above capillary filling pressure, resulting in ischemia"; microtrauma is another way of describing microcirculatory occlusion.

Yet another embodiment of Gassner et al is to treat wounds to enhance wound healing (see col. 2, line 4), wherein the amount of botulinum toxin administered includes about 5 units (see "7 units", col. 6, line 17; 20 units (see col. 8, lines 40-41), as well as amounts of botulinum toxin that treat wounds associated with skin, tendon, bone, inflammatory lesions, wounds caused by trauma, the treatment preventing the development of pressure sore at the pressure sites associated with bone, tendon and inflammatory lesions. The reduction of at least one symptom associated with wounds of skin, tendon, bone, inflammatory lesions and trauma are all encompassed by Applicant's definition provided at page 24 "treating" means "to alleviate (or to eliminate) at least one symptom of a pressure sore", which include "inflammation (see Instant Specification, page 3, paragraph 1)". Gassner et al therefore discloses a method of treating wounds to prevent pressure sores. Gassner et al inherently prevented the formation of pressure sores through reduction of inflammation at or near the site of the skin, bone, tendon or traumatic wound.

Therefore, Gassner et al anticipates the instantly claimed invention that administers botulinum toxin to a patient to treat or prevent a pressure sore through elevating at least one symptom associated with reduction or development of a pressure sore.

Conclusion

5. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

6. Barnes, MP (1999) is cited to show a correlation between brain injury spasticity (see page 935, paragraph 3) and the development of pressure sores (see page 936, paragraph 2)

7. Hawley (2002) is cited to show treatment of a large rectal ulcer with 20 units of botulinum toxin (see title).

8. McCarthy, V et al (2003) is cited to show the administration of botulinum toxin to assist in the prevention of pressure sores, also known as decubitus ulcers (see page 1729, col. 1, paragraph 3).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (571) 272-0862. The examiner can normally be reached on M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

VGP
November 29, 2004

Patricia A. Duffy
PATRICIA A. DUFFY
PRIMARY EXAMINER